REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1-51 and 69-73 were pending for purposes of this Office Action, as claims 52-68 were previously canceled in response to a Restriction Requirement.

Claims 1, 12, 17, and 34 are amended without prejudice in this Reply. Support for the amendment to claim 1 is found at paragraphs [0016] and [0093], as well as in Example 14 of the specification. Support for the amendment to claim 34 is also found in paragraph [0093] and in Example 14 of the specification. The amendments to claims 12 and 17 are redactions. It is respectfully submitted that no new matter has been added by virtue of these amendments.

Claims 24, 30, and 49 have also been amended to change their dependency to claim 12, as amended. Claims 47, 48, 51, 69, 70, and 72 are amended to change their dependency to claim 1, as amended.

Claims 18-23, 25-29, 39-46, 71 and 73 are canceled by the above amendments.

Claims 1-17, 24, 30-38, 47-51, and 69-70 and 72 remain pending.

Reconsideration is respectfully requested.

II. Double Patenting

The rejection of the claims on the ground of nonstatutory obviousness-type double patenting over co-pending U.S. Application No. 10/413,022 in view of U.S. Patent No. 5,476,093 and Noakes (Journal of Aerosol Medicine, 1995 Spring; 8 Suppl. 1:S3-7) has been maintained. Applicants respectfully submit that consideration will be given to the filing of a terminal disclaimer upon notification that the pending claims are otherwise allowable.

III. Claim Rejections- 35 U.S.C. § 103

In the current Office Action, claims 1-51 and 69-73 were again rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. 2002/0006933 to Gupta et al. ("the Gupta publication") in view of U.S. Patent No. 5,699,789 to Hendricks ("the Hendricks patent"); Ensuring Patient Care, 2nd ed., 1999, pages 15-21; U.S. Patent No. 5,476,093 to Lankinen ("the Lankinen patent"); Lucas et al., (Pharmaceutical Research, 1999; 16(10):1643-1647); and Noakes (Journal of Aerosol Medicine, 1995 Spring; 8 Suppl. 1:S3-7.

Applicants respectfully traverse the rejection and submit that the combination of references cited in the Office Action does not teach or suggest the present invention as now claimed. The amended claims are directed to a method for treating sexual dysfunction in a human via inhalation of a powder composition comprising a low dose of apomorphine (100-1600 μg), which is sufficient to provide a therapeutic effect in less than about nine minutes following inhalation, wherein the method is not associated with adverse side effects normally associated with administration of apomorphine.

The Gupta publication, US 2002/0006933, is concerned with treating sexual dysfunction using apomorphine. However, the Gupta publication, as shown in Example 2, discloses the administration of apomorphine by instillation (i.e., using a solution), as a *model* of inhalation. Thus, certain limitations are inherent in the teaching provided by the Gupta publication, and would not have made obvious the specific invention as now claimed in the subject application. For example, the Examiner's attention is directed to paragraph [0074] of the Gupta publication, where it is stated that "[a]n 8 mg human dose compares well with about 1.33 mg apomorphine dose in dogs." Accordingly, Applicants submit that the inhaled dose range described in the Gupta publication US 2002/0006933 is equivalent to a 3-12 mg human dose range – well above the 0.1-1.6 mg dose as claimed for the subject invention.

In addition, while pharmacokinetic parameters were presented in Example 2 of the Gupta publication, there were no pharmacodynamic data presented or even commented upon. Accordingly, there is nothing in the Gupta publication (which describes only the use of apomorphine solution, and only speculates that powder compositions can be used) that teaches or suggests that inhalation of apomorphine powder, at the doses tested, could achieve a therapeutic effect.

Certainly, the Gupta publication does not describe using a powder composition that can achieve a therapeutic effect within less than about nine minutes, as now claimed. As shown in Table 4 of the Gupta publication, the doses of apomorphine administered by "inhalation" (using instillation as a model) led to a C_{max} being achieved after 0.17 h, which is more than 10 minutes after administration. The subject application now claims "a therapeutic effect in less than about nine minutes." The rapid uptake of apomorphine into the blood following inhalation of the powdered formulations of the invention means that C_{max} is reached quickly. Thus, applicants believe the Gupta publication does not meet the limitations of low dose, rapid effect, and lack of associated side effects as recited for the claimed invention. Moreover, applicants believe there is no teaching or suggestion in US 2002/0006933 that would lead a person of ordinary skill in the art to modify what is described in the Gupta publication and thereby arrive at the claimed dose, time to therapeutic effect, and lack of associated side effects, as claimed.

A further feature recited in amended claim 1 is that inhalation of the dry powder composition comprising low-dose apomorphine is not associated with the adverse side effects normally associated with the administration of apomorphine. The rapid C_{max} which is reached by the subject invention, coupled with the short half-life that is associated with inhaled apomorphine, minimizes the period in which any side effects will occur. Data from the study described in Example 14 of the present application consequently show the powdered apomorphine inhaled by the patients to be essentially free of associated adverse effects.

This advantage provided by the subject invention is a vast improvement over the 'inhalation' of apomorphine reported in the Gupta publication, where nearly every subject in the study suffered emesis within the first five minutes after inhaling the drug (see Table 3). This adverse side effect occurred using the method described in the Gupta reference despite the fact that the study was clearly designed to show apomorphine administration did NOT produce this adverse side effect.

To further illustrate this point, it is noted that the Gupta publication shows the inhalation route of administration, itself, is a contributory factor in the incidence of emesis observed. For example, the inhalation of a dose of 1 mg apomorphine led to a C_{max} of 31.5 ng/ml (Table 4). The administration of 20 mg apomorphine by oral gavage led to a very similar C_{max} of 29.3 ng/ml (Table 6). All five dogs in the inhalation study suffered immediate emesis upon inhaling the dose of apomorphine (Table 3). In contrast, only two out of five dogs suffered immediate emesis following the oral dose of apomorphine (Table 5).

Thus, although paragraph [0035] of US 2002/0006933 suggests that apomorphine may be administered as a dry powder by inhalation, the skilled person clearly would not have been motivated to do this, on the logical assumption that it would invariably be accompanied by immediate emesis. The skilled person certainly would not have expected the benefits that are associated with the powder formulations of the invention, namely the rapid onset of a therapeutic effect, using a relatively low dose, yet without induction of the adverse side effects normally associated with the administration of apomorphine.

None of the other cited references (U.S. Patent No. 5,699,789 to Hendricks; Ensuring Patient Care, 2nd ed., 1999, pages 15-21; U.S. Patent No. 5,476,093 to Lankinen; Lucas et al., (Pharmaceutical Research, 1999; 16(10):1643-1647); and Noakes (Journal of Aerosol Medicine, 1995 Spring; 8 Suppl. 1:S3-7) cure these defects of the Gupta publication. Specifically, these other cited references fail to teach the administration by inhalation of a dry powder composition at a dose of between about 100 to about 1600 μg of apomorphine. In fact, while these other references are concerned with inhalation therapy, and are cited for describing similar particle size

ranges or propellants used for an inhalation composition, none of them relate to apomorphine or treatments for sexual dysfunction and thus cannot be readily adapted to, or readily applied to modify, the teaching of the Gupta publication in order to cure the defects of the primary reference.

Neither do these other cited references describe that such administration provides a therapeutic effect in less than about nine minutes without inducing the adverse side effects normally associated with the administration of apomorphine. A person skilled in the art concerned with the administration of apomorphine for the treatment of sexual dysfunction would therefore not find in these other cited references any teaching or suggestion regarding the relatively low dose and relatively rapid onset of therapeutic effect provided by the subject invention, which are claimed in the subject application, but are clearly missing from the Gupta publication.

The fact that inhalation of a dry powder comprising a low dose of apomorphine provides a therapeutic effect in less than about nine minutes, but is not associated with the adverse side effects normally associated with the administration of apomorphine, would not have been obvious from the Gupta publication, taken alone, or in combination with the other cited references. The skilled person would not have been motivated to substitute a dry powder composition for the solutions described in Example 2 and would not, therefore, have arrived at the methods as recited in the amended claims.

For the foregoing reasons, Applicants submit that the combination of the cited documents does not render the present claims obvious, and respectfully request withdrawal of the obviousness rejection under 35 U.S.C. § 103(a).

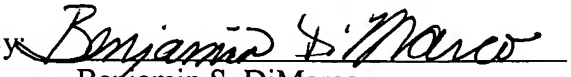
CONCLUSION

Reconsideration of the present application, as amended, is requested. The Examiner is respectfully requested to telephone Applicant's undersigned attorney in order to resolve any outstanding issues and advance the prosecution of the case to allowance.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

DAVIDSON, DAVIDSON & KAPPEL, LLC

By 

Benjamin S. DiMarco
Registration No. 50,129

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940